ARUP LABORATORIES | aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: 801-583-2787, toll free: 800-522-2787
Jonathan R. Genzen, MD, PhD, Chief Medical Officer

PATIENT REPORT

Patient Age/Sex: Unknown

Specimen Collected: 11-Sep-23 10:29

X-Cytogenomic SNP Microarray | **Received: 12-Sep-23 14:07** **Report/Verified: 12-Sep-23 14:13**

Procedure	Result	Units	Reference Interval
Cytogenomic SNP Microarray	**Abnormal** * f1 i1		[Normal]

Result Footnote

f1: Cytogenomic SNP Microarray
Test Performed: Cytogenomic SNP Microarray (CMA SNP)
Specimen Type: Peripheral blood
Indication for Testing: Congenital malformation of face and neck, microcephaly
---
RESULT SUMMARY
Abnormal Microarray Result (Female)

16p11.2 Proximal Duplication (BP4 to BP5 Region)

Classification: Pathogenic, Reduced Penetrance
Copy number change: 16p11.2 gain
Size: 540 kb

RESULT DESCRIPTION
This analysis showed an interstitial duplication (3 copies present) involving chromosome 16, within 16p11.2. This region contains at least 29 genes (listed below), including the gene TBX6.

This is a duplication of the 16p11.2 proximal (TBX6) region, involving recurrent breakpoints (BPs) within flanking low-copy repeat regions, BP4 and BP5. The reported size of this duplication may vary across studies due to variability in breakpoints within flanking repeat regions.

Please note this region is distinct from the recurrent 16p11.2 distal (SH2B1) region, which involves breakpoints BP2-BP3.

INTERPRETATION
Duplication of the 16p11.2 proximal (TBX6) region is associated with a variable clinical phenotype that may include developmental delays/intellectual disability (including speech), autism, behavioral difficulties, psychiatric disorders including schizophrenia, congenital anomalies, seizures, and other variable clinical findings.

The 16p11.2 proximal duplication shows incomplete penetrance. Expression of any phenotype associated with this duplication has been estimated to be 27.2 percent (17.4-40.7, 95 percent confidence interval) (Rosenfeld et al. 2013). This estimate does not define the risk for a specific phenotype but includes all levels of expression that have been observed amongst carriers of the duplication. It is significantly enriched in patients as compared to control populations.

One hypothesized explanation for the reduced penetrance and variable expressivity of copy number variants (CNVs) is that expression of clinical phenotypes may require a second hit in genes that affect the same developmental pathways. Although undefined, this second hit may be another CNV, a sequence variant, or involve environmental, epigenetic, or stochastic factors. Thus, in the absence of associated clinical findings, this CNV may represent a susceptibility factor for expression of associated phenotypes.

Duplications involving 16p11.2 are usually inherited, often from an unaffected or mildly affected parent. Parental testing is unlikely to determine if this CNV is clinically significant, as its presence or absence in a clinically unaffected parent or sibling will neither rule out nor confirm causality; however, it may be considered for recurrence risk counseling.

Recommendations:

Result Footnote

f1: Cytogenomic SNP Microarray
1) Genetic counseling
2) Parental testing for the duplication by genomic microarray analysis may be considered. This test is available, at a charge, through ARUP Laboratories. Please order test code 2003414, Cytogenomic SNP Microarray, and include the accession number for this case (23-173-146397).

Health care providers with questions may contact an ARUP genetic counselor at (800) 242-2787 ext. 2141.

References:
1) D'Angelo et al. Defining the Effect of the 16p11.2 Duplication on Cognition, Behavior, and Medical Comorbidities. JAMA Psychiatry. 2016 Jan;73(1):20-30. PMID: 26629640.
2) Steinman et al. 16p11.2 deletion and duplication: Characterizing neurologic phenotypes in a large clinically ascertained cohort. Am J Med Genet A. 2016 Nov;170(11):2943-2955. PMID: 27410714.
3) Rosenfeld et al. Speech delays and behavioral problems are the predominant features in individuals with developmental delays and 16p11.2 microdeletions and microduplications. J Neurodev Disord. 2010 Mar;2(1):26-38. PMID: 21731881.
4) Niarchou et al. Psychiatric disorders in children with 16p11.2 deletion and duplication. Transl Psychiatry. 2019 Jan 16;9(1):8. PMID: 30664628.
5) Coe et al. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat Genet. 2014 Oct;46(10):1063-71. PMID: 25217958.
6) Rosenfeld et al. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med. 2013 Jun;15(6):478-81. PMID: 23258348.
7) Girirajan et al. Phenotypic heterogeneity of genomic disorders and rare copy-number variants. N Engl J Med. 2012 Oct 4;367(14):1321-31. PMID: 22970919.
8) Unique: Understanding Rare Chromosome and Gene Disorders. (www.rarechromo.org)

Cytogenomic Nomenclature (ISCN):
arr[GRCh37] 16p11.2(29651576_30191848)x3

Genes in the 16p11.2 duplicated region:
SPN, QPRT, C16orf54, ZG16, KIF22, MAZ, PRRT2, PAGR1, MVP, CDIPT, CDIPTOSP, SEZ6L2, ASPHD1, KCTD13, TMEM219, TAOK2, HIRIP3, INO80E, DOC2A, C16orf92, FAM57B, ALDOA, PPP4C, TBX6, YPEL3, LOC101928595, GDPD3, MAPK3

Technical Information
- This assay was performed using the CytoScan(TM) HD Suite (Thermo Fisher Scientific) according to validated protocols within the Genomic Microarray Laboratory at ARUP Laboratories
- This assay is designed to detect alterations to DNA copy number state (gains and losses) as well as copy-neutral alterations (regions of homozygosity; ROH) that indicate an absence- or loss-of-heterozygosity (AOH or LOH)
- AOH may be present due to parental relatedness (consanguinity) or uniparental disomy (UPD)
- LOH may be present due to acquired UPD (segmental or whole chromosome)
- The detection sensitivity (resolution) for any particular genomic region may vary dependent upon the number of probes (markers), probe spacing, and thresholds for copy number and ROH determination
- The CytoScan HD array contains 2.67 million markers across the genome with average probe spacing of 1.15 kb, including 750,000 SNP probes and 1.9 million non-polymorphic probes
- In general, the genome-wide resolution is approximately 25-50 kb for copy number changes and approximately 3 Mb for ROH (See reporting criteria)
- The limit of detection for mosaicism varies dependent upon the size and type of genomic imbalance. In general, genotype mixture due to mosaicism (distinct cell lines from the same individual) or chimerism (cell lines from different individuals) will be detected when present at greater than 20-30 percent in the sample
- Genomic coordinates correspond to the Genome Reference Consortium human genome build 37/human genome issue 19 (GRCh37/hg19)

Result Footnote

f1: Cytogenomic SNP Microarray
Variant Classification and Reporting Criteria
- Copy number variant (CNV) analysis is performed in accordance with recommendations by the American College of Medical Genetics and Genomics (ACMG), using standard 5-tier CNV classification terminology: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign
- CNVs classified as pathogenic, likely pathogenic, or variant of uncertain significance are generally reported, based on information available at the time of review
- Known or expected pathogenic CNVs affecting genes with known clinical significance but which are unrelated to the indication for testing will generally be reported
- Variants that do not fall within the standard 5-tier CNV classification categories may be reported with descriptive language specific to that variant
- In general, recessive disease risk and recurrent CNVs with established reduced penetrance will be reported
- For a list of databases used in CNV classification, please refer to ARUP Constitutional CNV Assertion Criteria, which can be found on ARUP's Genetics website at www.aruplab.com/genetics
- CNVs classified as likely benign or benign that are devoid of relevant gene content or reported as common findings in the general population, are generally not reported
- CNV reporting (size) criteria: losses greater than 50 kb and gains greater than 400 kb are generally reported, dependent on genomic content
- ROH are generally reported when a single terminal ROH is greater than 3 Mb and a single interstitial ROH is greater than 10-15 Mb (dependent upon chromosomal location and likelihood of imprinting disorder) or when total autosomal homozygosity is greater than 3 percent (only autosomal ROH greater than 3 Mb are considered for this estimate)

Limitations
This analysis cannot provide structural (positional) information associated with genomic imbalance. Therefore, additional cytogenetic testing by chromosome analysis or fluorescence in situ hybridization (FISH) may be recommended.

Certain genomic alterations may not or cannot be detected by this technology. These alterations may include, but are not limited to:
- CNVs below the limit of resolution of this platform
- Sequence-level variants (mutations) including point mutations and indels
- Low-level mosaicism (generally, less than 20-30 percent)
- Balanced chromosomal rearrangements (translocations, inversions and insertions)
- Genomic imbalance in repetitive DNA regions (centromeres, telomeres, segmental duplications, and acrocentric chromosome short arms)

Data Sharing
In cooperation with the National Institutes of Health's effort to improve understanding of specific genetic variants, ARUP submits HIPAA-compliant, de-identified (cannot be traced back to the patient) genetic test results and health information to public databases. The confidentiality of each sample is maintained. If you prefer that your test result not be shared, call ARUP Laboratories at (800) 242-2787 ext. 3301. Your de-identified information will not be disclosed to public databases after your request is received, but a separate request is required for each genetic test. Additionally, patients have the opportunity to participate in patient registries and research. To learn more, visit ARUP's Genetics website at www.aruplab.com/genetics.

This result has been reviewed and approved by [redacted]

A portion of this analysis was performed at the following location(s):
[redacted]

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Test Information

i1: Cytogenomic SNP Microarray

INTERPRETIVE INFORMATION: CYTOGENOMIC SNP MICROARRAY

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.